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Wednesday, 29 June 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville MD 20852
USA

Dear Colleagues:

Re: Draft Guidance – Clinical Lactation Studies – Study design data analysis, and recommendations for labelling.

Firstly, we congratulate you and your colleagues for introducing these guidelines, which in our view are long overdue. Overall, we are very impressed with the breadth of the guidance and with the specific detail. We have a few comments listed below that we hope you will be prepared to consider:

Section III – dot point 4 –Line 147...include antipsychotics in the list of common marketed medications

Section A. Mother-Infant Pair Design – The aims of calculating bioavailability in the infant and or infant clearance are laudable but rarely practical.

Section B. Lactating Women Only Designs – Line 286
Subsection 2 – there is a suggestion that "diurnal variation" changes should be addressed – we are unaware of any information suggesting that this might be useful in this area of research – needs elaboration if included.

Subsection 6 – We are not convinced that the complete breast emptying strategy is the only way to get a satisfactory estimate of milk concentration and/or infant exposure via milk, even though we have used this strategy in our own research. It is in our view best suited to the single-dose milk study (eg anti-migraine drugs)

We would strongly suggest that you also include an option to collect representative milk samples (5-10 mL by pump or hand expression) each time the infant feeds during a dose-interval. This strategy is particularly useful when one is studying drugs that lactating mothers are taking chronically (eg antidepressants, antiepileptics). Our own current practice is to collect 6-8 samples over a 24 hour period. If the drug transfer into milk is likely to be affected by fat content of the milk, then we usually attempt to collect both pre-feed and post-feed samples at some or all of the times. Where this is not practicable, our

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view is that any sample is better than none. If the drug does not have a likelihood of being affected by lipid content, then we still ask the mum's to collect a representative sample that is approximately 50% each of pre- and post-feed milk.

Our article [1] on the "design of lactation studies" is informative in this area and we would also recommend you include it in your bibliography.

Section V Data analysis

A- parameter estimation – we suggest that you include the following equation immediately under your equation for "Estimated Daily Infant Dose";

Estimated Daily Infant Dose (mg/kg/day)= Average drug concentration in milk (mg/mL) x 150 mL/kg/day

We would also like to suggest that the % Maternal Dosage be renamed to the more common usage, Relative Infant Dose (RID) as is used by numerous authors in this field.

While your description of M/P ratio and its use is perfectly correct, it is very important to point out that M/P x average drug concentration in maternal serum is exactly equivalent to "Average drug concentration in milk". Indeed in out view, it is totally unnecessary to measure M/P. It is far better to just measure the average concentration in milk. This point needs to be emphasized as there is still much mis-interpretation in the literature about M/P and its clinical relationship to the potential for adverse effects.

Also, in this section we noted that you do not give any guidance on how to interpret infant dose as an absolute value or relative to the maternal dose. If this is important for the guidelines we suggest you consult various discussions we have contributed to the literature [1,2].

Section VI Labelling Part B Line 689

We would like to suggest two additional pieces of information be added

- Oral bioavailability in infant, if known.
- Normal clinical dose in infants if known.

Section VII Considerations for future research.

We were pleased that you had mentioned the possibility of active transport of drugs into milk and given 2 relevant references. While this area appears to be limited to a small group of drugs, we agree that it is well worth keeping in mind. In this regard we would suggest you also include an excellent paper that shows the range of transporters that are present in mammary epithelium [3].

Sincerely yours

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Bibliography

1. BEGG EJ, DUFFULL SB, HACKETT LP, ILETT KF: Studying drugs in human milk: time to unify the approach. *J. Hum. Lact.* (2002) **18**(4):319-328.

2. HALE TW, ILETT KF: In:*Drug therapy and breastfeeding. From theory to clinical practice.* The Parthenon Publishing Group, London (2002):1-94.

3. ALCORN J, LU X, MOSCOW JA, MCNAMARA PJ: Transporter gene expression in lactating and nonlactating human mammary epithelial cells using real-time reverse transcription-polymerase chain reaction. *J. Pharmacol. Exp. Ther.* (2002) **303**(2):487-496.

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Bibliography

1. BEGG EJ, DUFFULL SB, HACKETT LP, ILETT KF: Studying drugs in human milk: time to unify the approach. *J. Hum. Lact.* (2002) **18**(4):319-328.

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